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Risk of T-Cell Lymphomas in Persons With AIDS

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Summary: Lymphomas in persons with AIDS are mostly B-cell types, but T-cell lymphomas have also been reported. We examined T-cell lymphoma risk in the 2-year period after AIDS onset by linking 302,834 adults with AIDS to cancer registry data. Of 6,788 cases of non-Hodgkin's lymphoma (NHL) with specified histologies, 96 (1.4%) were T-cell lymphomas. Assessment was based on clinical diagnosis and histology because T-cell marker data were inadequate, but when present, marker data supported the T-cell diagnosis. The relative risk of T-cell lymphoma, estimated by standardized incidence ratio, was 15.0 (95% confidence interval: 10.0–21.7). Risks were increased for all subtypes, including mycosis fungoides, peripheral lymphomas, cutaneous lymphomas, and adult T-cell leukemia/lymphoma (ATLL). HIV-related immunodeficiency could be important, but differences between the population developing AIDS and the general population (e. g., immigration from the Caribbean region for ATLL) might independently increase T-cell lymphoma risk. **Key Words:** AIDS—HIV—T-cell lymphoma—Mycosis fungoides—Non-Hodgkin's lymphoma—Adult T-cell leukemia/lymphoma.

The high relative risk (RR) of non-Hodgkin's lymphoma (NHL) in persons with AIDS has been well documented (1–3) and NHL is accepted as an AIDS-related tumor (4) Most of these are high- and intermediate-grade B-cell lymphomas. However, T-cell lymphomas of various types have also been described (e.g., 5–8). At issue is whether these case reports reflect an increase in the risk of T-cell lymphomas or are merely observations of incidental cases in persons with AIDS. We used the AIDS-Cancer Match Registry to examine T-cell lymphoma risk in AIDS patients.

METHODS

We linked AIDS and cancer registry data from 1978 through 1996 in 11 state or metropolitan areas of the United States: Atlanta (GA), Connecticut, Florida, Illinois, Los Angeles (CA), Massachusetts, New Jersey, New York state, San Diego (CA), San Francisco (CA), and Seattle (WA). Methods have been described elsewhere in detail (9). Matches were done under strict confidentiality guidelines, approved by each registry, under which only locally authorized registry representatives saw any personal identifiers. Overall, 366,034 AIDS patients were linked to local area cancer records. Linkages to cancer registry data were sought only for persons with AIDS diagnosed when the local cancer registry was functioning, thus including 309,365 persons with AIDS. Cancer information was used only for the periods when both AIDS and cancer registry data were complete. In all, 83% were men, of whom 48% were white, 32% were black, and 19% were Hispanic; exposure to HIV was predominantly by homosexual/bisexual contact (62%) and injecting drug use (26%). Among females, 21% were white, 57% were black, and 21% were Hispanic; by HIV exposure route, 47% were injecting drug users, and 34% were infected through heterosexual activity. These distributions are similar to those of national data on persons with AIDS reported to the U. S. Centers for Disease Control and Prevention (CDC) (10). The current analysis focuses on 302,834 adults with AIDS (15–69 years old at AIDS diagnosis).

We considered NHL, regardless of type, in an HIV-positive person to be diagnostic of AIDS and therefore reset the AIDS onset date when NHL was recorded in cancer registry data, if it was within 5 years before the AIDS registry onset date. Therefore, by definition, no cases preceded AIDS. Medical attention becomes intense around the time of an initial AIDS diagnosis. To reduce ascertainment bias from the detection of previously undiscovered or nascent lymphoma, we excluded NHL cases occurring within 3 months of reported AIDS onset. Although cancer cases linked to AIDS are likely to be accurate throughout the course of AIDS, the number of study subjects under observation is

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progressively less clear because of the possibility of unrecorded deaths and movement from the catchment areas. Given that the expected number of cancers is derived from the denominator of persons under observation, we limited the follow-up period to 4 to 27 months after AIDS onset.

Lymphoma diagnoses were defined according to the *International Classification of Diseases for Oncology,* 2nd edition, (ICD-O-2) (11). Histology codes considered as T-cell types included mycosis fungoides/Sézary syndrome (9700/3 and 9701/3), peripheral (9702/3 through 9707/3), and cutaneous lymphomas (9709/3), as well as adult T-cell leukemia/lymphoma (ATLL) (9827/3) and angiocentric T-cell lymphomas (9713/3). We analyzed data recorded about T- and B-cell immunohistochemistry markers, when they were available in the cancer registry data, to determine whether these diagnoses were consistent in attributing the lymphoma to the T-cell types. Measures of risk examined incidence and RR from standardized incidence ratios, with 95% confidence intervals (CI) based on the Poisson assumption. Expected cases were derived from contemporaneous age-, gender-, and race-specific rates in the underlying populations. Because expected cases include the AIDS-related cases, the resulting RRs are conservative. Proportions were compared using the χ^2 test or, when numbers were small, the Fisher exact test (two-sided p values).

RESULTS

From 1978, 120,114 NHLs occurred in persons between 15 to 74 years old in cancer registry data, of which 10,592 NHLs (9%) were linked to persons who had AIDS diagnosed between 15 and 69 years old. Among all NHL cases, 24,945 (21%) had nonspecific histologies (ICD-O-2 codes 9590/3–9595/3), whereas among AIDS-linked NHLs, 3,804 (36%) had nonspecific NHL histologies. Of the AIDS-NHLs, 5,968 (56%) occurred at AIDS onset, 3,405 (32%) occurred 4 through 27 months after AIDS onset, 1,100 (10%) occurred 28 to 60 months after AIDS onset, and 119 (1%) occurred more than 60 months after AIDS onset (Table 1).

T- and B-cell Immunohistochemistry Markers

Of all NHLs reported to cancer registries in the 1980s, 8% had marker data, whereas in the 1990s, 29% had marker data. Eleven percent of 3,804 nonspecific AIDS-NHLs had immunohistochemistry marker data, of which 45 (11%) of 402 had T-cell markers (Table 2). In comparison, 24% of 6,692 specified non-T-cell NHL histologies had marker data, of which 173 (11%) also had T-cell markers. Finally, 96 NHLs were classified as specific T-cell histology types, which constituted 1% of all AIDS-linked NHLs (1.4% of those with specified types). Among the 96 NHLs with specific T-cell histologies, 49 (51%) had marker data, of which 46 (94%) had T-cell markers.

The 96 AIDS-linked T-cell NHLs included 35 cases of mycosis fungoides (including 1 Sézary syndrome), 36 peripheral T-cell lymphomas, 13 cutaneous lymphomas, 11 ATLLs, and 1 angiocentric T-cell lymphoma (Table 1). Among those with marker data, T-cell markers were reported for 75% of mycosis fungoides (6 of 8), 100% of 27 peripheral lymphomas, 83% of cutaneous lymphomas (5 of 6), and 100% of 8 ATLLs. Three lymphomas (3%) with T-cell histologies were recorded as having B-cell markers. Because of the incompleteness of the immunohistochemistry data and the possibility of nonrandom assessment of surface markers between AIDS and non-AIDS patients with lymphomas, we used only the histologic diagnosis to assign patients as having T-cell lymphomas.

Risk of T-Cell Lymphomas

In the period at or within 3 months of AIDS onset, 59 T-cell lymphomas were recorded (Table 1). The RR in this period cannot be estimated reliably because NHLs, including T-cell types, were included to define AIDS onset. During the 4 to 27 months after AIDS onset, which we regard as the most reliable cohort follow-up period, 28 T-cell NHLs were diagnosed. An additional 9 cases occurred in the period between 28 months and 60 months after AIDS onset, but none of the 119 lymphomas diagnosed more than 60 months after AIDS onset was recorded as having a T-cell lymphoma histology.

TABLE 1. *Non-Hodgkin's lymphomas (NHL) occurring in 302,834 adults with AIDS*

	AIDS-relative time				
	0 to 3 mo.	4 to 27 mo.	28 to 60 mo.	≥60 mo.	
T-cell lymphoma (%)	59 (61)	28 (29)	9 (9)	0 (—)	96 (100)
Mycosis fungoides/Sézary	25	8	2	0	35
Peripheral lymphoma	21	10	5	0	36
Cutaneous lymphoma	4	7	2	0	13
Adult T-cell leukemia/lymphoma	9	2	0	0	11
Angiocentric T-cell lymphoma	0	1	0	0	1
Specified non–T-cell types (%)	4,111 (61)	1,877 (28)	625 (9)	79 (1)	6,692 (100)
Nonspecified types (%)	1,798 (47)	1,500 (39)	466 (12)	40 (1)	3,804 (100)
All NHL (%)	5,968 (56)	3,405 (32)	1,100 (10)	119 (1)	10,592 (100)

TABLE 2. *T- and B-cell marker data on non-Hodgkin's lymphoma (NHL)*[a] in adults with AIDS

	N	Marker data (%)	B[b] (%)	Null[b] (%)	T[b] (%)
Specified, T-cell	96	49 (51)	3 (6)	0 (—)	46 (94)
Specified, non–T-cell	6,692	1,617 (24)	1,430 (88)	14 (0.9)	173 (11)
Non-specified	3,804	402 (11)	349 (87)	8 (2.0)	45 (11)
All NHLs	10,592	2,068 (19)	1,782 (86)	22 (1.1)	264 (13)

[a] Includes adult T-cell leukemia/lymphoma.
[b] Percentage refers to the proportion of those with immunohistochemistry data.

This proportional distribution of T-cell lymphomas was similar to that of the specified non–T-cell lymphomas (Table 1).

In the 4 to 27 month period after AIDS onset, 238,411 adults with AIDS were followed for 308,349 person years (py), which averages 1.3 years per person. The RR of developing T-cell lymphoma was 15.0 (95% CI, 10.0–21.7). Increases were statistically significant for all specific T-cell subtypes (Table 3), varying from eightfold for mycosis fungoides/Sézary syndrome to 24.4-fold for cutaneous lymphomas. However, as shown in Table 3, incidence rates in the cohort followed into the 4 to 27 months after AIDS onset were similar for mycosis fungoides and cutaneous and peripheral T-cell lymphomas (2.3 to 3.2 per 100,000 py). The larger variation in RR for these subtypes (8-fold to 24-fold) was attributable to differences in the expected number of cases of the disease. Two of the 11 ATLL cases occurred in the 4 to 27 months after AIDS onset. Although the RR of ATLL, 14.6-fold, was similar to those seen for other T-cell lymphomas, ATLL incidence, 0.65 per 100,000 py, was lower.

The RR of T-cell lymphoma in the 4- to 27-month period after AIDS onset was higher in Hispanics (RR, 24.0; 95% CI, 8.8–52.3; $n = 6$) than in white (14.4; 95% CI, 6.9–26.6; $n = 10$) or black patients (10.0; 95% CI, 4.6–19.1; $n = 9$), although the incidence in persons with AIDS was fairly similar by race/ethnicity (10.3, 7.0, and 8.7 per 100,000 py, respectively). Cases were seen in every age group, but absolute incidence increased with age. RR by age was fairly stable because the background incidence also increased with age. Although the incidence was higher in men than women with AIDS (9.6 and 6.2 per 100,000 py, respectively), RRs were 14.9 and 15.9, respectively, and the male:female incidence ratio (1.5:1) was about the same as that seen in T-cell lymphoma patients without AIDS (1.7:1).

Within HIV-exposure category (Table 4), 25% of the 96 patients with T-cell lymphoma were injecting drug users/blood product recipients, compared with 17% of all 10,592 NHL patients with HIV-infection ($p = .04$). In contrast, 62% of those with T-cell lymphomas were homosexual/bisexual men with HIV infection versus 72% of all NHLs ($p = .03$). When ATLL cases were excluded, the difference between homosexual/bisexual men and others was no longer significant ($p = .31$), but the difference between drug- and blood-infected persons and those infected by other exposure routes remained statistically significant ($p = .02$). The lymphomas in drug users were most commonly classified as peripheral T-cell types.

Cases of ATLL were different from other diagnosis groups in several ways. Eight (73%) of the 11 ATLL cases were black, compared with 28 (34%) of 82 non-ATLL T-cell lymphoma types ($p = .02$). Race was unknown in three non-ATLL NHLs. Four (36%) of 11 ATLL patients were women, whereas among other T-cell lymphomas, only 5 (6%) of 85 were women ($p = .009$).

TABLE 3. *Observed (Obs.) and expected (Exp.) rates of lymphomas in the 2-year period after AIDS onset. (Incidence and relative risks (RR) with 95% confidence intervals (CI) are also provided.)*

	No. of cases		Incidence[a]			
	Obs.	Exp.	Obs.	Exp.	RR	95% CI
T-cell lymphomas	28	1.87	9.22	0.61	15.0	10.0–21.7
Mycosis fungoides/Sézary	8	1.01	2.59	0.33	8.0	3.4–15.7
Peripheral lymphoma	10	0.41	3.24	0.13	24.3	11.7–44.8
Cutaneous lymphoma	7	0.29	2.27	0.09	24.4	9.8–50.3
Adult T-cell leukemia/lymphoma	2	0.14	0.65	0.04	14.6	1.8–52.8
Angiocentric T-cell lymphoma	1	0.03	0.32	0.01	35.9	0.9–200.0
All non-Hodgkin's lymphomas	3,405	47.0	1,104.3	15.2	72.4	70.0–74.9

[a] Per 100,000 person-years.

TABLE 4. *HIV-exposure categories of persons developing non-Hodgkin's (NHL) lymphoma*

	Homosexual/bisexual men	Injected drug user/ blood product recipients[a]	Heterosexuals	Other/unknown
T-cell lymphomas (%)	60 (62)	24 (25)	6 (6)	6 (6)
Mycosis fungoides/Sézary (%)	27 (77)	7 (20)	0 (—)	1 (3)
Peripheral lymphoma (%)	20 (56)	12 (33)	2 (6)	2 (6)
Cutaneous lymphoma (%)	10 (77)	3 (23)	0 (—)	0 (—)
Adult T-cell leukemia/lymphoma (%)	3 (27)	1 (9)	4 (36)	3 (27)
Angiocentric T-cell lymphoma (%)	0 (—)	1 (100)	0 (—)	0 (—)
All NHL (%)	7,657 (72)	1,803 (17)	583 (6)	549 (5)

[a] Predominantly injecting drug users; homosexual/bisexual men who also used injected drugs were classified with homosexual/bisexual men.

There was a higher likelihood that persons with ATLL were HIV-infected heterosexually ($p = .001$) or had unknown exposure routes than other subtypes ($p = .005$).

DISCUSSION

These findings show that persons with AIDS are at increased risk of T-cell lymphomas. More NHLs had nonspecific histologies than was seen in the general population, possibly reflecting less adequate evaluation or more difficulty in interpretation of the histology. As expected, the specified lymphomas in persons with AIDS were predominately B-cell types. However, the RR of T-cell lymphoma was increased 15-fold. The increase applied to all T-cell lymphoma types, including mycosis fungoides/Sézary syndrome, peripheral lymphomas, cutaneous lymphomas, and ATLL. Among non-ATLL types, incidence rates were similar, and variation in RR appeared to be due mostly to differences in the expected rates.

The etiology of lymphomas is generally unknown. In the AIDS setting, the huge increase in B-cell lymphomas cannot be related to HIV directly, inasmuch as HIV does not infect B-cells. We have speculated that genetic errors occurring during proliferation in response to T-cell dysregulation may be responsible (1). In the general population, most but not all T-cell lymphomas have a CD4 phenotype (12). We had no information about the T-cell phenotype in our cases. Case reports describe both CD4 and CD8 phenotype lymphomas in persons with HIV/AIDS (e. g., in references 5–8), but there are no series large enough to document whether the phenotype distribution differs from that in the general population.

HIV targets CD4-bearing lymphocytes and might be expected to kill many such cells. However, only a portion of CD4 cells is HIV-infected at any time. A direct role was suggested for HIV in T-cell lymphomagenesis, based on a single case in which HIV was found to be integrated at a clonal site (8). In the setting of HIV-related immunosuppression, other oncogenic viruses could be involved. Epstein-Barr virus has been suggested as important (7,13) and the possible role of the HTLV is considered below. Groups at high risk of HIV also have other environmental exposures related to their lifestyles. This increased prevalence of other factors may contribute to T-cell lymphoma incidence in persons with AIDS, either in conjunction with immunosuppression or independently.

The difficulty in establishing causal relationships is illustrated by the excess of ATLL. The unusual distribution of ATLL by gender, race, and HIV-exposure group suggests environmental influences on persons with AIDS. Outside of the AIDS setting, ATLL is well established to have a strong association with HTLV type I (HTLV-1) (14–16). Although the HTLV-1 infection status of our ATLL cases was unknown, positive HTLV-1 antibody status is likely to have been confirmed as part of the diagnosis. HTLV-1 is more frequent in women and is endemic in areas such as the Caribbean and sub-Saharan Africa (14). We had no data on the place of birth of our study subjects. However, the excess of ATLL that we observed in women and black individuals with AIDS could indicate that the AIDS subgroups getting ATLL were at high risk of this cancer because they came from an HTLV-1–endemic area. The high proportion of ATLL patients infected heterosexually or with an unknown route of HIV exposure adds further support for an unusual risk profile. We cannot exclude the possibility that HIV infection might have increased their risk of developing ATLL. However, ATLL risk has not been shown previously to be higher in persons with AIDS, even though there are occasional reports of ATLL in persons with HIV/AIDS in HTLV-1 endemic areas (16).

A closely related retrovirus, HTLV- II, is found in high frequency among injecting drug users (15). This virus has been reported in 2 HIV-positive patients with a severe erythrodermic desquamative skin disease (17) and was recently found to be clonally integrated in cells of a cutaneous CD8-positive T-cell lymphoma in an intravenous drug user in the United States (5). Those investi-

gators noted that only rarely are persons with T-cell lymphomas of any kind found to be HTLV-1nfected, within or outside of the HIV setting (5). In our study, T-cell lymphomas were proportionally more frequent than expected in persons HIV-infected through injecting drug use/blood exposure. Almost all these persons were injecting drug users. The difference was small but statistically significant even when ATLL cases were excluded. We cannot determine whether this association was related to HIV–HTLV-2 coinfection because we had no information about HTLV status. However, we suggest that this result may have occurred not because the risk of T-cell NHL was high in injecting drug users but because the risk of all NHL was low. Injecting drug users are predominantly black. The rate of NHL is known to be low in both HIV-infected and uninfected groups within the black population (1).

The validity of the data needs careful attention. We had no access to reviewing the original clinical records or the histology. Specific histology was recorded for only 64% of the NHL cases and T-cell histology types might also have occurred among those missing specific histology. We could not address the frequency of T-cell lymphomas based solely on immunohistochemistry data because only 19% of NHLs had such data and testing of samples might have been biased by AIDS status. Of 2,010 cancers with non–T-cell histologies and marker data, 220 (11%) had T-cell markers. If lymphomas with marker data available were representative of all lymphomas, many more T-cell lymphomas were in the non–T-cell group than in the specified T-cell subtypes. Cutaneous lymphomas can be of B-cell origin (6). However, the available data on B- and T-cell markers supported the ICD-O-2 classification we used to define T-cell lymphoma types, inasmuch as 94% of those with marker data were confirmed as having T-cell markers.

These limitations probably resulted in conservative RR estimates. Because of missing information, it is likely that many more T-cell lymphomas occurred than we documented. Although study subjects with and without AIDS both had inadequately described NHL records, incomplete histologic descriptions were more frequent in study subjects with AIDS. Several factors may have contributed, including less complete patient evaluations, greater difficulty with reading the histology in persons with an HIV-dysregulated lymphoid system, and differences in reporting practices.

Potential biases also exist against a true association. Persons with AIDS might have independent risk factors that increased their T-cell NHL risk. It might be speculated that the increased risk of ATLL, for example, occurred because those born in countries in the Caribbean basin were independently at higher risk of HIV and of HTLV-1. However, the higher RR of other T-cell lymphomas was present even when ATLL cases were excluded. For these other T-cell lymphomas, no independent risk factors are known. Finally, HIV-infected persons can develop pseudolymphomas, which include polyclonal T-cell peripheral blood proliferations (18) or cutaneous T-cell infiltrates (19,20). These cases might have been erroneously reported as T-cell lymphomas.

In summary, T-cell lymphomas appear to be part of the spectrum of lymphomas increased in persons with AIDS. However, the RR appears to be considerably lower than that for B-cell NHLs. Their histologies span the T-cell subtypes, including mycosis fungoides, ATLL, and peripheral and cutaneous lymphomas. This diversity of types suggests that a common factor, presumably dysregulation of the immune system, might account for the excess risk. Whether HIV itself plays any role in the etiology of T-cell lymphomas cannot be determined from these data.

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APPENDIX

The following are contributors to the AIDS Cancer Match Registry: *National Cancer Institute, Bethesda, Maryland:* Robert Biggar, Morten Frisch, Eric Engels, James Goedert; Oak Ridge National Laboratories, Oak Ridge Tennessee: Tim Borges, Bob Stafford, P. Y. Lu; *Information Management Systems, Silver Springs, Maryland:* Tim McNeel, Kathryn Schleeter, Steve Scoppa.

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